ROLE OF COX-2 IN THE CARDIOVASCULAR SYSTEM

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Prostaglandins have diverse roles in the heart and vasculature, including proinflammatory effects and vasodilation. COX-2 catalyzes the conversion of prostaglandin precursors to prostacyclin, a key vasoactive substance involved in regulation of vascular tone and perfusion. The adverse-effect profile of NSAIDs in patients with compromised cardiac function can include increased systemic vascular resistance and reductions in cardiac output, renal blood flow, and glomerular filtration (Dzau et al, 1984; Townend et al, 1995; Vane et al, 1998). In addition, prostaglandins produced by COX-2 may have a role in promoting tissue repair following injury.

COX-2 EXPRESSION

COX-2 is generally believed to be an inducible enzyme in cardiac and vascular tissues (Holmes et al, 1997; Rimarachin et al, 1994; Wong et al, 1998), although one recent in vitro study suggests that COX-2 may be constitutively expressed in rat aorta (Connolly et al, 1998). However, COX-2 knockout mice exhibit diffuse myocardial fibrosis in both ventricles and mild cardiac myofiber dropout, indicating that COX-2 deficiency may be implicated in cardiomyopathy (Dinchuk et al, 1995) and that COX-2 itself may be cardioprotective (Wu, 1998).

In a study in humans, COX-2 was not identified in hearts from healthy controls, but was identified in the myocytes and inflammatory cells of infarcted myocardial tissue in patients with heart failure secondary to sepsis or ischemic heart disease (Wong et al, 1998). In patients with heart failure secondary to dilated cardiomyopathy, COX-2 was found in fibrotic cardiac tissue, but not in myocytes or inflammatory cells.

In rabbit aorta, high-density lipoprotein (HDL) has been demonstrated to induce COX-2 expression (and increase levels of the vasodilator, prostacyclin) in smooth muscle cells (Viñals et al, 1997).

USE OF SELECTIVE COX-2 INHIBITORS IN ANIMAL MODELS

The effects of a selective COX-2 inhibitor and a nonselective COX-1/COX-2 inhibitor (indomethacin) on vascular contractility of endothelium-denuded aorta were assessed in a murine model (Connolly et al, 1998). Both agents blocked α-agonist-induced vasoconstriction, presumably due to inhibition of COX-2. The authors speculated that COX-2 was produced constitutively in rat aorta because the experimental procedures were undertaken before the extracted tissue would have been able to induce and express the isoform.

In another preclinical study, dogs were given intravenous doses of indomethacin, 6-MNA, or a selective COX-2 inhibitor (Brooks et al, 1998). Neither 6-MNA nor indomethacin altered baseline heart rate or blood pressure, but the selective COX-2 inhibitor caused significant bradycardia (-24 bpm ± 5%) without changes in blood pressure.

HYPOTHETICAL APPLICATION TO HUMANS OF PRECLINICAL RESULTS IN THE CARDIOVASCULAR SYSTEM

Available data on COX-2 expression in infarcts and cardiomyopathy suggest that COX-2 has a role in both inflammation and repair. Complete suppression of COX-2, as in knockout mice, may have further implications than inhibiting inflammation and may, in fact, inhibit repair. This may lead to excessive fibrosis and deleterious consequences in patients with cardiac or vascular injury.

COX-2 also appears to be involved in the control of vascular tone, participating in HDL-induced production of vasodilatory prostaglandins and α-agonist-induced vasoconstriction. The consequences of inhibiting these effects remain to be determined, but could have long-term implications.

ROLE OF COX-2 IN THE RESPIRATORY TRACT

ROLE OF COX-2 IN THE RESPIRATORY TRACT

The use of NSAIDs in asthmatic inflammatory conditions is controversial because inhibition of cyclooxygenase isoenzymes may increase production of leukotrienes and enhance airway responsiveness, worsening asthmatic symptoms (Szczeklik, 1983). COX-1 and COX-2 both catalyze the conversion of arachidonic acid to prostaglandin, and inhibition of either enzyme may increase leukotriene production. In addition to these effects on arachidonic acid metabolism, recent findings have demonstrated that COX-2 is involved in a variety of physiologic and regulatory processes in the pulmonary system.

COX-2 EXPRESSION

Although COX-2 has a role in some noninfectious inflammatory processes in the respiratory tract (Fernández-Morata et al, 1997; Kato et al, 1998; Vadas et al, 1996), it also may have distinct regulatory functions under physiologic conditions. In animals, constitutively expressed COX-2 has been isolated from the lung (Brannon et al, 1998; Charette et al, 1995; Ermert et al, 1998). In rats, both cyclooxygenase isoforms are detected in the lungs (Ermert et al, 1998). COX-2 is noted primarily in macrophage and mast cells, smooth muscle cells of partially muscular vessels, large veins of the hilum, and bronchial epithelial cells. Extensive localization of COX-2 in the rat lung suggests that it has a physiologic, as well as an inflammatory, role in the respiratory tract. In the guinea pig, COX-2 expression is responsible for maintaining intrinsic tone in the trachea (Charette et al, 1995).

In fetal and newborn sheep lungs, COX-2 mRNA expression increased during the fetal to 1-week-old period (Brannon et al, 1998). However, COX-2 protein was not detected in the developing ovine lung. There is no evidence that COX-2 knockout mice exhibit pulmonary pathology (Dinchuk et al, 1995).

In the cultured human airway smooth muscle cell, COX-2 is not expressed under control conditions. However, COX-2 expression is stimulated by proinflammatory cytokines and bradykinin, and expression is inhibited by dexamethasone and both selective and nonselective COX-2 inhibitors (Belvisi et al, 1997; Pang and Knox, 1997a, 1997b; Vigano et al, 1997).

High levels of COX-2 mRNA are present in the normal human lung, whereas levels of COX-1 are approximately twofold lower (O'Neill and Ford-Hutchinson, 1993). In patients with stable asthma and chronic bronchitis, both cyclooxygenase isoforms are found in respiratory epithelium, but COX-2 is not upregulated (Demoly et al, 1997). In upper respiratory mucosa of patients with chronic allergic rhinitis and sinusitis and in control patients, COX-1 and COX-2 are expressed in the epithelium and neither enzyme is upregulated during this noninfectious inflammation (Demoly et al, 1998). Both cyclooxygenase isozymes are expressed in nonstimulated epithelial cells isolated from nasal polyps (Kowalski et al, 1997). Therefore, constitutive expression of COX-2 in the lungs, and its failure to increase in the presence of noninfectious inflammation, suggests a more basic, homeostatic role, rather than one restricted to supporting inflammation.

In one interesting study, lung fibroblasts from patients with idiopathic pulmonary fibrosis did not respond to inflammatory stimuli (eg, PMA, lipopolysaccharide, IL-1) with increased COX-2 expression or activity (Wilborn et al, 1995). Because one of the effects of prostaglandin E_2 is to inhibit fibroblast proliferation and collagen synthesis, the authors postulated that the inability of these patients to upregulate COX-2 and increase prostaglandin production might inhibit reparative processes, allowing more opportunity for fibroblasts to lay down connective tissue and promoting the development of pulmonary fibrosis. They further suggested that "potential detrimental consequences might result from pharmacologic inhibition of COX-2, at least during the reparative phases of inflammatory injury in the lung" (Wilborn et al, 1995).

USE OF SELECTIVE COX-2 INHIBITORS IN ANIMAL MODELS

In isolated guinea pig trachea, a selective COX-2 inhibitor and indomethacin were used to evaluate effects on intrinsic tone (Charette et al, 1995). Both agents reversed intrinsic tone, with the selective COX-2 inhibitor exhibiting greater effect, implying that COX-2 is responsible for maintaining intrinsic tone in the trachea.

HYPOTHETICAL APPLICATION TO HUMANS OF PRECLINICAL RESULTS IN THE RESPIRATORY TRACT

Constitutive expression of COX-1 and COX-2 in the human lung clearly suggests that there is a role for these isoenzymes in maintaining normal, homeostatic functions. Furthermore, in patients with asthma or noninfectious rhinitis and sinusitis, COX-2 expression is not upregulated, as would be expected in inflammatory conditions, providing further support for a noninflammatory role for this isozyme. The consequences of inhibiting these unknown functions remain to be determined. The observation that patients with idiopathic pulmonary fibrosis are unable to induce COX-2 expression in the lung raises the question of whether selective inhibition of COX-2 might inhibit the reparative phases of inflammatory injury in the lung, or otherwise contribute to the development of fibrosis.

ROLE OF COX-2 IN THE PANCREAS

ROLE OF COX-2 IN THE PANCREAS

Both COX-1 and COX-2 have been shown to be expressed in acinus cells of the pancreas in rats, both during normal conditions and during pancreatitis (Zabel-Langhennig et al, 1998). However, in pancreatic islet beta cells from hamsters, rats, and humans, COX-2 was recently shown to be constitutively expressed whereas minimal, if any, COX-1 is expressed (Sorli et al, 1998). COX-2 was also predominant during interleukin-1-stimulated conditions. The clinical relevance of these data, if any, to use of selective COX-2 inhibitors is unknown.

LITERATURE SEARCHES

CONDUCTED TO DEVELOP

THIS DOCUMENT

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The literature searches completed to develop this document were performed by Grace Johnson, PharmD, who is an Editor with Scientific Therapeutics Information, Inc, a medical communications company. Searching qualifications of Dr Johnson include training and experience received during the Doctor of Pharmacy program at the University of Michigan, an American Society of Health-System Pharmacists-accredited pharmacy practice residency completed at the University of Florida, and 3 years performing medical writing and editing as an Associate Editor or Editor with Scientific Therapeutics Information, Inc.

Online literature searches were conducted in MEDLINE (1966-1998), EMBASE (1980-1998), and BIOSIS (1997-1998), with MEDLINE being the primary reference source. All searches were limited to English language. MEDLINE search strategy included the following terms: COX-2 inhibitors, cyclooxygenase-2 inhibitors, cyclo-oxygenase-2 inhibitors, meloxicam, celecoxib, SC-58635, flosulide, nimesulide, SC-58125, L-748731, L-745337, SC-57666, T-614, cyclooxygenase-2 and renal, cyclooxygenase-2 and lung, cyclooxygenase-2 and inflammation, cyclooxygenase-2, COX-2, and cyclooxygenase 2 with wound healing, immune system, or hormone. EMBASE search strategy included the following terms: COX-2 inhibitor, cyclooxygenase-2 inhibitor, cyclo-oxygenase-2 inhibitor, cyclooxygenase-2 and renal, cyclooxygenase-2 and inflammation, cyclooxygenase-2, COX-2. BIOSIS search strategy included the following terms: cyclooxygenase-2, COX-2, cyclooxygenase 2.

Additional reference sources were used when available, including references cited in publications related to this topic. Recent issues of *Gastroenterology*, *Journal of Rheumatology*, *Arthritis and Rheumatism*, and *American Journal of Gastroenterology* were reviewed for abstracts presented at the following annual meetings: Digestive Disease Week (1998), Panamerican Congress of Rheumatology

(1998), American College of Rheumatology (1997), and American College of Gastroenterology (1998), respectively.

Only selected references were used in the development of this document. Although many references were reviewed, only those cited herein are listed in the reference list at the end of the document. All cited references are available from SB upon request.

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EXECUTIVE SUMMARY

Celecoxib (tradename Celebrex™) is an oral anti-inflammatory and analgesic product intended for use in the treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) and for the management of pain. It was developed to provide anti-inflammatory and analgesic effects comparable to commonly used non-steroidal anti-inflammatory agents drugs (NSAIDs) but without the gastrointestinal and platelet effects of NSAIDs. The clinical development program for celecoxib included more than 13,000 patients and healthy volunteers enrolled in over 50 different studies. The overall results of this clinical program demonstrated that celecoxib is comparable in efficacy to naproxen and is superior to naproxen, diclofenac and ibuprofen in the occurrence of upper gastrointestinal (UGI) ulceration, ulcer complications and effects on platelets. Further, celecoxib was not found to be associated with increases in other clinically significant adverse reactions compared to NSAIDs. Thus, celecoxib has been shown to provide a significant therapeutic benefit over commonly prescribed NSAIDs used in the treatment of OA, RA and pain.

Celecoxib is a highly selective inhibitor of cyclooxygenase-2 (COX-2), one of two known isoforms of cyclooxygenase: COX-1 and COX-2. Commonly used NSAIDs such as aspirin, naproxen and ibuprofen are non-selective inhibitors of COX-1 and COX-2. (1) They are effective anti-arthritic agents but produce clinically-limiting side effects due to their inhibition of COX-1 at therapeutic doses. (2-4)

The clinical program examined the human pharmacokinetics, efficacy, and safety profile of celecoxib with a focus on its effects on the GI tract, platelets and kidney.

Celecoxib is a low solubility, high permeability drug that is rapidly absorbed, has a large volume of distribution (consistent with high tissue uptake) and is extensively metabolized by the liver to inactive metabolites that are excreted primarily in the feces and to a lesser extent in the urine. Pharmacokinetics are linear; the elimination half life is about 10 hours and steady state levels are reached by five days with the therapeutic dose and regimen. The pharmacokinetics in subgroup populations such as the elderly were studied and well described. No clinically significant drug-drug interactions were observed with compounds commonly used by the intended patient population, including warfarin and methotrexate.

Five pivotal trials of 6 or 12 weeks duration uniformly showed that celecoxib was superior to placebo in treating OA of the knee and/or hip and similar to a full therapeutic dose of naproxen. Maximal efficacy was obtained with 200 mg per day administered as a single dose or divided doses. Replicate 12-week studies showed that celecoxib at 100 mg or 200 mg BID was superior to placebo in treating RA and similar to naproxen. A 6-month trial confirmed the durability of response with celecoxib. The data from four

trials using an acute post-surgery pain model and the chronic pain data from the aforementioned arthritis trials collectively demonstrated that celecoxib has analgesic properties. The post-oral surgery studies showed that celecoxib had an onset of action within one hour and significant relief of OA pain was demonstrated within 24 hours after the first dose.

Over 4,500 patients with OA or RA participated in endoscopy trials designed to compare the incidence of UGI ulceration between celecoxib, NSAIDs and placebo. In two 12-week studies with Baseline and end-of-study endoscopies, the ulcer incidence with celecoxib at full therapeutic doses, as well as at 2-4 times the full therapeutic dose, was not significantly different from placebo but significantly lower than with naproxen. The superior GI safety of celecoxib compared to naproxen was confirmed by a 12-week serial endoscopy trial. Another 12-week serial endoscopy study demonstrated a significantly lower ulcer incidence with celecoxib compared to ibuprofen and a 6-month trial showed a significantly lower incidence of ulcers with celecoxib compared to diclofenac.

The endoscopy results were corroborated by a blinded tabulation of clinically significant UGI events (bleeding, perforation, and gastric outlet obstruction) that occurred during controlled studies. The analysis demonstrated an annual incidence of ulcer complications for celecoxib of 0.20% that was significantly less than the 1.68% seen with NSAIDs, but similar to placebo. The incidence of clinically significant UGI events for celecoxib was confirmed by an analysis of data from a large open-label safety trial.

Celecoxib was also differentiated from NSAIDs in terms of its effects on platelets, that contain only the COX-1 isoform. At doses up to 6-12 times the full therapeutic dose, celecoxib had no significant effect on platelet aggregation or bleeding time. In contrast, NSAIDs consistently and significantly inhibited platelet aggregation and prolonged bleeding time at typical therapeutic doses.

The safety of celecoxib was evaluated based on the experience with all the patients and healthy subjects who participated in clinical trials. Chronic dosing in arthritis patients ranged from 100 mg BID to 400 mg BID for periods in excess of 12 months. A dose as high as 1200 mg BID was used in certain safety/pharmacology studies. Total exposure exceeds 3,000 patient years and 981 patients have completed at least one year of treatment. Overall, celecoxib was well tolerated. GI symptoms (dyspepsia, nausea, abdominal pain) were more common in patients receiving celecoxib than in patients on placebo, but significantly less than in patients on NSAIDs. Renal adverse events were uncommon and occurred no more frequently than in patients on NSAIDs. Clinical laboratory test results indicated that celecoxib did not have adverse hematologic or hepatic effects.

In sum, celecoxib is equivalent to NSAIDs in terms of therapeutic effectiveness (a function of the inhibition of COX-2), but lacks the characteristic COX-1 dependent toxicities of NSAIDs on the GI tract and platelets. In general, celecoxib was safe and well tolerated. These results clearly establish the wide clinical therapeutic index of celecoxib and clinical utility of this new agent in the treatment of OA, RA, and pain.

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